IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket No.: FUERTES-LOPEZ

In re PATENT Application of:	)	
	)	
LAURA FUERTES-LOPEZ &	)	**Examiner: Anne Maria**
MARCOS TIMÓN-JIMENEZ	)	**Sabrina Wehbe**
	)	
Appl. No.: 10/816,591	)	**Group Art Unit: 1633**
	)	
Filed: April 1, 2004	)	**Confirmation No.: 8510**
	)	
For: DNA EXPRESSION CONSTRUCT FOR THE TREATMENT OF INFECTIONS WITH LEISHMANIASIS	)	

BRIEF OF APPEAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION OF EFS-WEB TRANSMISSION

I hereby certify that this paper is being EFS-Web transmitted to the U.S. Patent and Trademark Office, Alexandria VA 22313-1450, on OCTOBER 9, 2009.
Date

Ursula B. Day
(Name of Registered Representative)

(Signature) Oct. 9, 2009 (Date of Signature)

S I R:

This is an appeal from the final rejection of claim 24 by the Primary Examiner. The Brief is being filed under the provisions of 37 C.F.R. §41.37. The amount of $270.00 to cover the requisite fee set forth in 37 C.F.R. §41.20(b)(2) is being paid herewith by credit card.

The Commissioner is hereby also authorized to charge fees which may be required, or credit any overpayment to Deposit Account No. 50-1747.

(1) REAL PARTY IN INTEREST

The above-referenced patent application has been assigned to MOLOGEN AG with a place of business at Fabeckstrasse 30, 14195 BERLIN Germany, the real party in interest by virtue of an assignment which was recorded in the Patent and Trademark Office under reel 014303 and frame 0931.

(2) RELATED APPEALS AND INTERFERENCES

There are no and there have been no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

The following claims are in the proceedings:

Claim 24 not allowed.

The following claim is on appeal:

Claims 24.

Claim 24 stands rejected under 35 U.S.C. §103(a) as being unpatentable over as being unpatentable over J. Exp. Med., Vol. 186 (7), 1137-1147, 1917 ("Gurunathan") in view of U.S. Patent No. 6,451,593 to Wittig ("Wittig") and further over Makkerh (1916) Current Biology, Vol. 6 (8), 1025-1027 (1916) to Makkerh ("Makkerh").

The claim is in the appendix.

(4) STATUS OF AMENDMENTS

A Request for Reconsideration but no amendments after final were filed. In the Advisory Action following the reconsideration, the Examiner remained with her position.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 24 refers to a vaccine for vaccinating a living being against infections by Leishmania, (specification page 5/6, lines 20-29/1-8. A DNA expression construct comprising covalently-closed, linear deoxyribonucleotide molecules, (specification p.5, lines 20-28; page 6, lines 1-8), said deoxyribonucleotide molecules each comprising a linear double-stranded region (specification p.5 lines 23-24); said double-stranded region comprising single strands being linked by short, single-stranded loops of deoxyribonucleic acid nucleotides (specification p. 5, line 26); said double strand-forming single strands comprising: a terminator sequence, (specification p. 6, line 1); and a coding sequence encoding at least the p36 LACK antigen under control of a promoter sequence and operable in the living being to be immunized (specification p. 5, line 28- p. 6, line 1; said DNA expression construct being covalently linked to at least one oligopeptide to increase transfection efficacy, (specification p.6, line 15-21; said at least one oligopeptide consisting of the amino acid sequence of SEQ ID 3 (specification p. 6, lines 22-25; and sequence listing SEQ ID NO 3).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Issue 1 - Whether claim 24 is patentable under 35 U.S.C. §103(a) over Gurunathan in view of Wittig and Makkerh.

(7) ARGUMENT

a) THERE IS NO MOTIVATION FOR THE PERSON SKILLED IN THE ART NOR IS IT FOUND IN GURUNATHAN TO MODIFY IT USING WITTIG AND MAKKERH

The invention

The invention resides in the combination of the MIDGE DNA construct encoding p36 antigen attached to the NLS, here PKKKRKV, and used as a

vaccine against Leishmania major ("Leishmania").

The vaccine against infections of Leishmania includes the claimed DNA expression construct covalently linked to sequence PKKKRKV, thereby increasing transfection. Upon determining the total IgG antibody titer in trial mice, this vaccine brings superior results measured as the highest titer of circulating antibody as compared to the known vaccines and the vaccines used in the controls. An increase of 11% in protection against Leishmania can be seen in FIG. 2 when compared with, for example, the group vaccinated with p36/rVV.

The Prior Art

Gurunathan tries to immunize against Leishmania by inserting cDNA for the cloned Leishmania antigen LACK into a eukaryotic expression vector, a plasmid.

Significantly, the use of plasmids was described in applicant's disclosure as a drawback which the present invention tries to overcome (specification p 4, 2.full paragraph) since it is well known to the ordinary person skilled in the art that the use a eukaryotic plasmid expresses, in addition to wanted protein, other types of proteins that are undesirable and are expressed, for example immunostimulatory sequences. Therefore, the skilled artisan would not reasonably choose to start out with that teaching.

Wittig teaches an expressible nucleic acid construct (MIDGE) which contains only sequence information necessary for expressing a gene for RNA or protein synthesis.

The Makkerh reference refers to an investigation into NLS tolerance to mutation. Nothing in the reference shows using the claimed NLS.

There is no motivation provided by Gurunathan to modify the DNA vaccine that meets claim 24 under appeal in the present application. In fact, Gurunathan motivates one skilled in the art to improve its DNA vaccine in an opposite manner as to what has been set forth in the present invention.

Obviously, the "motivation factor" has been discussed at length in verbal and written dialogs between the Examiner and applicant in this particular application. Applicant wishes to point out that motivation, suggestion, teaching is

not abolished by the U.S. Supreme Court as the Examiners seems to believe. A year ago, an expanded panel of this honorable Board held in a precedential decision that in order to show obviousness, one of ordinary skill in the art would have had some reason to modify a known product in the fashion claimed, *Ex parte Whalen* (BPAI July 23, 2008). Under that holding, the modification of Gurunathan through Wittig lacks the necessary motivation and is thus untenable.

Gurunathan focuses on the induction of IL-12 and IFN-γ production as an essential part of the protective immune response, as mentioned on page 1142, left column,

> *"mice that controlled infection (LACK DNA plus or minus IL-12 DNA or LACK protein plus rIL-12) made substantial amounts of IFN-γ in response to LACK protein, whereas non-healing mice had no detectable IFN-γ."*

And further, also on page 1142, left column,

> *"vaccinated mice treated with anti-IL-12 had a striking inhibition of in vitro production of IFN-γ (Fig. 8 B), suggesting that LACK DNA induced protective immunity through IL-12–dependent production of IFN-γ."* (Emphasis added)

It is therefor unreasonable to assert that it is obvious to modify the technology disclosed in Gurunathan by applying a technology that is contrary to what is suggested within Gurunathan itself. Furthermore, this clearly renders the success of the MIDGE vaccine as unexpected, as the 'modification' of Gurunathan carried out in the present invention went against both suggested enhancement and common knowledge in the field, and still produced an efficient vaccine.

While Wittig teaches the potential disadvantages of excess DNA sequences of bacterial origin in expression vectors, the teaching of Gurunathan portrays such DNA sequences as useful, and even essential, in generating the protective immune response. When trying to develop or improve the prior art as disclosed in Gurunathan, one skilled in the art would not refer to Wittig, as the

teaching of Wittig to reduce bacterial vector sequences contradicts the teaching of Gurunathan. Therefore, the combination of Gurunathan and Wittig is an artificial product of *ex post facto* analysis, identifiable by the clearly conflicting themes evident in these two very distinct documents.

b) **THE EXAMINER'S ANALYSIS OF THE GURUNATHAN REFERENCE IS BASED ON ERRONEOUS INTERPRETATION OF THE SCIENCE OF GURUNATHAN**

Gurunathan teaches plasmid DNA vaccination against Leishmania in mice but focuses on the induction of IL-12 and IFN-γ production.

The Examiner has noted that the data presented in Gurunathan shows expression of LACK antigen from a plasmid leads to IFN-γ induction and a specific immune response. Additionally, the empty plasmid (without coding sequence for the LACK antigen) stimulates no such immune response. The Examiner therefore concludes at the top of page 3 of the Advisory Action, that:

> "*The skilled artisan reading Gurunathan et al. could only conclude that it is the LACK DNA itself and not the bacterial DNA that induces IFN-gamma and results in the generation of a therapeutic immune response...*" (emphasis added)

From this statement it appears that a significant misunderstanding of the scientific material is evident on the part of the Examiner, who believes we have argued that the immune response was caused solely by the bacterial DNA. This is not the case. It was never asserted by the applicant that Gurunathan teaches non-coding bacterial DNA as being solely responsible for IFN-γ induction and generation of a therapeutic immune response.

The Examiner has only considered two experimental conditions in her analysis of Gurunathan, subsequently biasing her interpretation of the results. The Examiner has compared treatment with LACK DNA (plasmid expressing

LACK DNA) to treatment with control DNA (empty vector), and concluded that the empty vector has no effect.

However, considering the control experiment 'control DNA' alone (as the Examiner has done) is insufficient to examine whether the bacterial vector DNA plays a role in the immune response. Even though bacterial vector DNA alone produces no immune response, the full data set indicates that LACK antigen only has an immune stimulating function when present with bacterial vector DNA.

Figure 1 demonstrates the measurement of foot pad swelling, or infection, of infected BALB/c mice after immunization with:

- (open square): LACK DNA (plasmid expressing LACK DNA)
- (open diamond): Control DNA (plasmid without any insert LACK DNA)
- (open circle): LACK protein (no DNA administered)
- (open triangle): LACK protein + rIL-12

The results show that:

- LACK DNA expressed from a plasmid vector induces therapeutic immune response.
- Control DNA plasmid induces NO therapeutic immune response.
- IMPORTANTLY, LACK protein alone induces NO therapeutic immune response.
- LACK protein + rIL-12 induces therapeutic immune response.

These results clearly demonstrate that LACK antigen (administered as protein or expressed from a plasmid) only generates immune response in the presence of either bacterial vector DNA, or rIL-12.

This result is reproduced in other experiments shown in Figure 2, Figure 5A, Figure 6B and Figure 7. In each of these experiments the LACK antigen, when administered as protein alone, provides a very similar result to the empty vector. It is the combination of LACK DNA with bacterial vector sequence which stimulates the immune response. This is clearly stated by the authors of

Gurunathan, in the passages cited in our previous response, and in the second sentence of the introduction:

> "*The mechanism by which DNA vaccination is able to generate these potent immune responses appears to be through the induction of various proinflammatory cytokines elicited in response to certain immunostimulatory sequences (ISS) contained in the bacterial plasmid*".

Such a statement is in direct opposition to the technology disclosed in Wittig; which teaches essentially the removal of all unnecessary vector DNA. Therefore the combination of Gurunathan and Wittig does not lead to the desired result, no matter how the data is considered. One skilled in the art would not even have attempted, let alone expected to succeed, using the technology from Wittig to create a vaccine after reading Gurunathan.

c) A REFERENCE HAS TO APPLY IN ITS ENTIRETY

Furthermore, in this context the case *In re Hedges* 228 U.S.P.Q. 685 (1986) applies where it was determined that it is impermissible to pick only part of a reference to support any given position, to the exclusion of other parts necessary to the full appreciation of what the reference suggests to one skilled in the art. The Examiner has chosen to ignore the reference to the potential importance of bacterial vector DNA, essentially using only one part of Gurunathan to form her arguments. The Examiner has only focused on the comparison between LACK DNA and empty vector DNA control, while ignoring the LACK protein control treatments. Taken as a whole, the lesson of Gurunathan would not encourage one skilled in the art to remove all bacterial vector DNA sequences from the expression vector, as has been carried out in following the lesson from Wittig.

d) THE APPLICATION OF THE PKKKRKV NLS WAS NOT OBVIOUS FROM EITHER WITTIG OR MAKKERH

Wittig teaches that peptide chains can be covalently coupled to expression constructs in order to facilitate crossing of the endosomal membrane and nuclear localisation (Wittig et al, column 5). However, Wittig does not teach the specific peptide sequence claimed as SEQ ID NO: 3 in the present invention. Wittig proposes 3 distinct peptides that could be added to DNA expression constructs; the "nuclear localization sequence from SV40", the "signal peptide from HIV-gp41", and the "23 N-terminal amino acids of haemagglutinine". Use of SEQ ID NO: 3 as a covalently attached NLS peptide in the present invention is not disclosed by Wittig.

The Examiner asserts that the Makkerh reference

If the peptide coupling as taught by Wittig is applied directly to Gurunathan, various outcomes, and thus uncertainty, arises. It is not predictable which of the 3 proposed peptides would have lead to success. The selection of one of the 3 proposed alternatives cannot be seen as the substitution of one functional equivalent for another, as asserted by the Examiner. Due to the obviously significant difference in the 3 proposed peptides, and the uncertainty in applying any of the three, the selection of the SV40 NLS is not a functional substitution but an inventive step.

In considering thus the obviousness rejection, it is irrelevant whether or not the exact NLS peptide sequence was already known (Makkerh). The crucial selective step for the skilled practitioner is to decide from the 3 variants proposed in Wittig, a choice that only leads to uncertainty due to the insufficient disclosure in regards to likely success, and the sequence details of the various peptides.

e) THE DECLARATION OF DR. TIMON-JIMENEZ IS SUFFICIENT AND DEMONSTRATES UNEXPECTEDNESS

In order to demonstrate that the combination of LACK antigen, MIDGE expression vector technology and NLS peptides with the sequence of SEQ ID NO: 3 generated unexpected results, a declaration was made by one of the inventors Dr. Timon-Jimenez. The Examiner has asserted that the declaration is

deficient in two respects. Firstly, that the evidence of unexpected results is not commensurate in scope with the claimed product. Here the Examiner points out that SEQ ID NO: 3 refers to PKKKRKV, whereas the paper referred to by Dr. Timon-Jimenez (Lopez-Fuertes et al. (2202) Vaccine, Vol. 21, 247-257) uses an NLS sequence of PKKKRKVEDPYC. Secondly, that the results demonstrated are in fact not "unexpected" and that greater, or greater than additive effect is not necessarily sufficient for "unexpectedness". Thirdly, the Examiner disregarded the references that were supportive of the science as set forth in Dr. Timon-Jimenez' declaration.

(i) The Examiner failed to take into account references to support scientific statements made in the declaration of Dr. Timon-Jimenez that the functional unit of the NLS sequence is identical in the claimed invention and Fuertes-Lopez et al.

In regards to the first point, the functional unit or the basic peptide of the NLS sequence as applied in the present application is identical to that as referred to by Dr. Timon-Jimenez in the declaration (Lopez-Fuertes et al). As has been demonstrated through genetic approaches, the functional unit of the SV40 NLS is PKKKRKV, which has been shown to be the core requirement for function as a nuclear localisation signal (Kalderon et al, A short amino acid sequence able to specify nuclear location, 1984, Cell 39, 499-509, submitted herewith). Mutations made in and around this defined sequence have demonstrated that the SV40 NLS as stated in SEQ ID NO: 3 is the minimal functional NLS (Kalderon et al., Sequence requirements for nuclear location of simian virus 40 large-T antigen, 1984, Nature 377, 33-38, of record). Additions to the required NLS sequence can be found in the literature, such as PKKKRKVEDPYC. This sequence has been used in various papers, and such papers are clearly referenced in Lopez-Fuertes (for example reference 27 in Lopez-Fuertes: Zanta et al, Gene delivery: a single nuclear localization signal peptide is sufficient to carry DNA to the cell nucleus, 1999, Proc Natl Acad Sci USA, 96(1):91–6, of record). This simply constitutes the SV40 NLS with a non-functional additional linker sequence, namely EDPYC.

While the present wording of the amended claim 24 limits the NLS sequence of the present invention to only PKKKRKV due to the wording "consisting of" (which was suggested by the Examiner in one interview as means to avoid the references) this does not detract from the NLS being functional equivalents of each other since the sequence EDPYC is known to be non-functional and thus, the declaration of unexpectedness is of commensurate scope with the claimed invention.

ii. The results obtained through the use of MIDGE were unexpected, not due to greater effect, rather due to the application of a distinct expression system with complex features

In regards to the unexpected nature of the results, the Examiner references multiple passages in Lopez-Fuertes. In doing so, the Examiner points out, and accurately so, that the results obtained through the use if the MIDGE-based vaccine of the present invention (MIDGE-p36-NLS/ MIDGE-p36-NLS) were comparable to the previously known prior art (pMOK-p36/ rVVp36).

As is clearly stated by the Examiner herself, the demonstration of 'greater effect' is not necessarily relevant to 'unexpectedness', because indeed greater effects can be expected. Therefore, we are not able to follow the reasoning of the Examiner in her argument that **'comparable effect'** as shown in the present case demonstrates **'expectedness'**.

The present invention claims a DNA vaccine that has an effectiveness comparable to older known methods, while the DNA vaccine according to the invention is easier to both produce and apply.

However, the issue of expectedness depends not on the comparison of success to older methods, but on the complexity of the attempt, and what would be held to be relevant by one skilled in the art during the development of the present invention. All skilled practitioners in molecular medicine are aware that the replacement of a traditional plasmid with another expression system, namely the application of similar expression machinery in the context of an entirely distinct kind of vector, immediately creates uncertainty as to the likelihood of success.

Generating protective immunity is a complex process, depending on many steps from the administration of DNA expression vectors until the protective immune response. It may have been known that the expression of the p36 antigen from a plasmid vector lead to protective immunisation, but the application of MIDGE and an SV40 NLS peptide demonstrates a clearly novel combination of complex features that surely involves uncertainty when viewed in light of the complexity of the immune system. For these reasons the success of the MIDGE DNA vaccine was indeed unexpected, as declared by Dr. Timon-Jimenez.

Furthermore, the application of MIDGE (essentially a reduction of all DNA sequence unnecessary for antigen expression) would have actually reduced the likelihood of generating a comparable immune response for one skilled in the art (Gurunathan). The removal of non-essential, but immune stimulatory, sequences would be predicted to generate a weaker immune response than full plasmid vectors. Because MIDGE produced a comparable immune response without the non-essential, immune stimulatory sequences, it is likely that the MIDGE vaccine functions via an alternative mechanism or pathway when compared to prior art. For this reason alone, the expectation of success is remote, as would be well understood by a skilled practitioner.

iii Applicant's claim 24 is directed to a vaccine that must be operable in a living subject

Applicant addresses the Examiner's statement on page 2 of the Advisory Action date July 10, 2009, in which the Examiner notes that applicant's claim is a product claim and not a method claim so that the preamble for the use as a "vaccine for vaccinating a living being against infection of Leishmania" carries no patentable weight. Claim 24 is directed to a vaccine where *inter alia*, "....a coding sequence encodes at least the p36 LACK antigen under control of a promoter sequence and operable in the living being to be immunized". Insofar as the vaccine has to be operable in a living being, it is believed to confer patentable weight.

CONCLUSION

Appellant has invented a vaccine against Leishmania which includes a DNA expression construct that has no extraneous bacterial or excess DNA sequences of bacterial origin and has a NLS sequence which eases transfection.

The cited prior art does neither teach nor suggest the essential features as defined in claim 24 of the present invention but merely shows compounds which at some point may disclose an element of the present invention but not the novel and inventive combination. The question of obviousness is, however, not whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed. (In re Sernaker, 702 F.2d 989, 217 U.S.P.Q 1, C.A.F.C. 1983).

When considering the arguments set forth by the Examiner in the final rejection, appellant believes that the Examiner misinterpreted the science in Gurunathan relying on hindsight in reaching his obviousness determination. As the C.A.F.C stated in W.L. Gore, 721 F.2d at 1553, 220 U.S.P.Q. at 312-313) "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher". Thus, the use of hindsight reconstruction to pick and choose among the references is impermissible.

For the above stated reasons, it is respectfully submitted that the rejection of the claim 24 issued by the Examiner on the references should be reversed.

Respectfully submitted,

By: _____
Ursula B. Day
Attorney for Appellant
Reg. No.: 47,296

Date: October 9, 2009
708 Third Avenue
Suite 1501
New York, N.Y. 10118
(212) 244-5500
UBD: sh

(8) CLAIMS APPENDIX

24. (Rejected) A vaccine for vaccinating a living being against infections by leishmania, the said vaccine comprising:

a DNA expression construct comprising covalently-closed, linear deoxyribonucleotide molecules;

said deoxyribonucleotide molecules each comprising a linear double-stranded region;

said double-stranded region comprising single strands being linked by short, single-stranded loops of deoxyribonucleic acid nucleotides;

said double strand-forming single strands comprising:

a terminator sequence, and

a coding sequence encoding at least the p36 LACK antigen under control of a promoter sequence and operable in the living being to be immunized;

said DNA expression construct being covalently linked to at least one oligopeptide to increase transfection efficacy;

said at least one oligopeptide consisting of the amino acid sequence of SEQ ID 3.

(9) EVIDENCE APPENDIX

NONE

(10) RELATED PROCEEDINGS APPENDIX

NONE